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Article

Correlation of ApoE Gene Polymorphism with Coronary Heart Disease Severity in Patients with Acute Coronary Syndrome Who Receive Statin Therapy, Padang, Indonesia

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A B S T R A C T

Coronary Heart Disease (CHD) is still the most common cause of death. Ischemic heart disease causes more than 7 million (12.8%) deaths worldwide. It is estimated that 3,750,000 Indonesians have CHD. CHD is a disease with many risk factors. ApoE gene polymorphism is associated with atherosclerosis and plays a role in lipid metabolism, which is 2-16% affecting variability in LDL levels. This study aims to look at the relationship between ApoE gene polymorphism and the severity of coronary heart disease. Data regarding ApoE gene polymorphism was obtained using polymerase chain reaction (PCR). DNA was isolated from white blood cells using DNA purification kit. ApoE2, ApoE3, ApoE4 alleles were detected by DNA sequencing. Data on the severity of coronary heart disease were obtained from angiography and were calculated based on SYNTAX scores. In this study, ApoE was obtained with e2 allele frequencies (4.63%), e3 (78.70%), and e4 (16.67%) with E2 / 2 (0%), E2 / 3 (3.70%), E2 / 4 (5.56%), E3 / 3 (64.81%), E3 / 4 (24.07%), and E4 / 4 (1.85%). The relationship between the SYNTAX score and the ApoE genotype has no significant difference. ApoE3 / 4 genotype has the highest SYNTAX score and the e4 allele has the most influence on CHD despite the influence of statin therapy..

I. INTRODUCTION

Coronary heart disease (CHD) is still the most common cause of death (Go et al., 2013). WHO (2008) states that ischemic heart disease causes more than 7 million (12.8%) deaths worldwide. In the United States (US), CHD is the cause of 1 in every 6 deaths in 2009 based on data from the American Heart Association (AHA) (Go et al., 2013; Ng et al., 2012). It is estimated that 3,750,000 Indonesians have CHD (Badan Penelitian dan Pengembangan Kesehatan, 2013). Despite a decrease in body-specific mortality rates from CHD in the last few decades, ischemic heart disease is now the leading cause of death worldwide, and it is estimated that CHD cases will increase in the coming decades with an increasingly shifting burden to low socio-economic groups. By 2020, it is estimated that this disease will be responsible for a total of 11.1 million deaths worldwide (Badan Penelitian dan Pengembangan Kesehatan, 2013; Mathers et al., 2006).

CHD is a disease with many risk factors. Individual factors with genetic predisposition to atherosclerosis have an important risk for developing CHD especially at a young age. The relationship between vascular wall function and severity of CHD is rather difficult to study. Examination of DNA variations such as ApoE polymorphism is one way to see the relationship. ApoE gene polymorphism is associated with atherosclerosis and plays a role in lipid metabolism, which is 2-16% affecting the variability of LDL levels (Elmadbouh et al., 2013). ApoE is a plasma glycoprotein and helps lipoproteins be removed from the circulation. The integral relationship between cholesterol homeostasis and removal of lipoproteins from the circulation is closely related to ApoE function as a ligand for cell surface receptors from the family of low density lipoprotein receptors. The binding properties of ApoE receptors are strongly influenced by differences in specific amino acid isoforms and the state of protein lipids. With the growing understanding of ApoE as a structural component of circulating plasma lipoproteins, the development of increasingly advanced neurobiology has revitalized interest in apoE (Haan et al., 2010).

There is currently no research on this gene polymorphism in Indonesia. This study aims to determine the relationship of ApoE gene polymorphism to the severity of coronary heart disease in patients with acute coronary syndrome undergoing cardiac catheterization at Dr. M. Djamil'S Hospital, Padang. This study aims to look at the relationship between ApoE gene polymorphism and the severity of coronary heart disease.

II. METHODS

This study is an analytical study with data collection carried out by cross sectional. It was conducted at Dr. M. Djamil's Hospital Padang, Biomedical Laboratory Faculty of Medicine, Andalas University and the Department of Pharmacology and Therapeutics, Faculty of Medicine Andalas Univeristy in June - November 2017. It involved acute coronary syndrome patients underwent catheterization at the Dr. M. Djamil's Hospital. This study was approved by the Faculty of Medicine, Universitas Andalas, Padang, Indonesia, ethics committee in 2017.

Data were collected from medical records of all inpatients in the Heart Section of Hospital with a diagnosis of acute coronary syndrome and undergoing cardiac catheterization. From the medical records of the patients, data were collected including demographic characteristics / data (name, age, gender, weight, medical record number, CHD risk factors), history results, physical examination results, results of initial laboratory examination, diagnosis and treatment of patients. Examination of current blood sugar, HbA1c, lipid profile and routine hematological profile was performed for the initial scans of patients who will be recruited in the study. Data regarding ApoE gene polymorphism was obtained from PCR examination conducted at the Biomedical Laboratory of Faculty of Medicine, Andalas University by using patient's blood sample. Blood

samples were taken from patients prior to catheterization. Blood samples were collected and stored at -20°C, and PCR examination was carried out together after the sample is satisfied.
Examination of this polymorphism uses polymerase chain reaction (PCR). DNA was isolated from white blood cells using DNA purification kit. ApoE2, ApoE3, ApoE4 alleles were detected by DNA sequencing. Assessment of the severity of CHD was done using SYNTAX scoring. SYNTAX Score (SYNergy between PCI with TAXUS™ and Cardiac Surgery) is an angiographic scoring system that assesses the complexity of CHD. The SYNTAX score is calculated by a computer program consisting of sequential and interative self-guided questions (Hauser et al., 2011).

III. RESULTS

Subject characteristics (Table 1).

Table 1. Subject characteristics

Basic characteristics	All research subjects f (%)	SYNTAX		p-value
		≤ 22 f (%)	> 22 f (%)	
Gender				
Male	49 (90.7%)	19 (38.8%)	30 (61.2%)	0.957
Female	5 (9.3%)	2 (40%)	3 (60%)	
Age (mean ± SD)	56.69 ± 8.90	57.15 ± 5.27	58.26 ± 12.5	0.696
Body Mass Index (mean ± SD)	23.5 ± 2.2	23.1 ± 2.01	2.9 ± 2.5	0.252
Risk Factors				
Smoking (n=65)	40 (74.1%)	15 (37.5%)	25 (62.5%)	0.723
Hypertension (n=65)	29 (57.3%)	9 (31%)	20 (69%)	0.504
Dyslipidemia (n=40)	31 (88.6%)	12 (38.7%)	19 (61.3%)	0.664
Family History (n=65)	8 (14.8%)	3 (37.5%)	5 (62.5%)	0.93
Menopause (n=2)	2 (3.7%)	1 (50.0%)	1 (50.0%)	0.743
Laboratorium's data				
Hemoglobin (mean ± SD)	13.2 ± 1.5	13.6 ± 1.7	13.3 ± 1.6	0.482
Total Cholesterol (mean ± SD)	188.6 ± 64.5	174.7 ± 39.4	207.4 ± 70.8	0.247
HDL (median, min-max)	38.5 (14-87)	34 (14-47)	39 (22-87)	0.333
LDL (mean ± SD)	125.03 ± 50.5	118.5 ± 37.7	133 ± 60.6	0.364
Trigliserida (mean ± SD)	134.7 ± 49.9	130.2 ± 52.6	141.2 ± 51.5	0.574
GDS (mean ± SD)	126.7 ± 24.9	131.1 ± 32.5	122.9 ± 21.5	0.500

Table 1 showed there was no statistically significant based on gender, age, body mass index, risk factors and laboratorium's data between SYNTAX score ≤22 and > 22 (p>0.05).
Level of lipid on each ApoE allele in CHD patients (Figure 1).

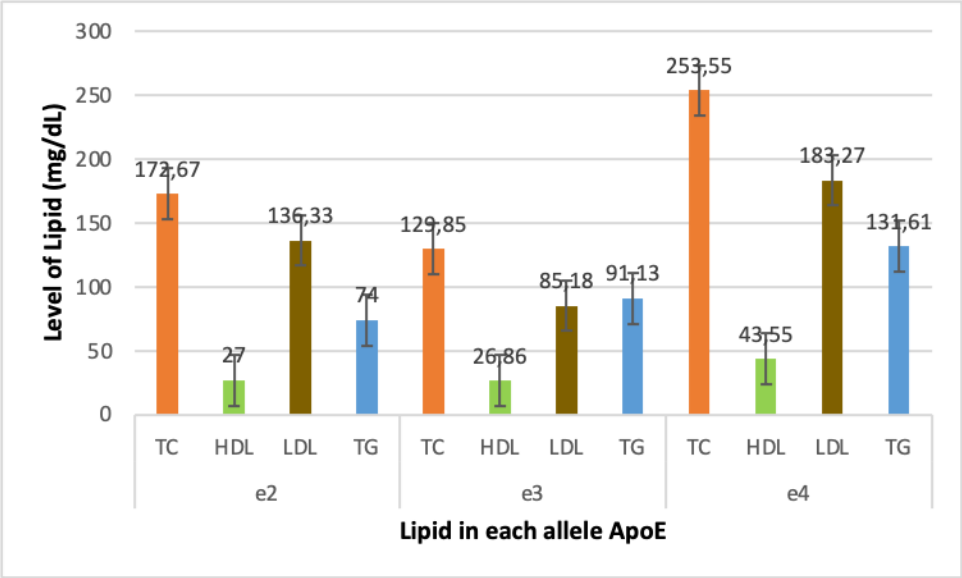

Figure 1. Level of lipid on each ApoE allele in CHD patients.

Figure 1 showed ApoE is a functional polypomorphism protein and encoded by three alleles, e2 (Cys112 / Cys158), e3 (Cys112 / Arg158), and e4 (Arg112 / Arg158). Each ApoE isoform has a different effect on lipoprotein metabolism. There are differences in lipid levels in the ApoE gene allele.

Description of SYNTAX score in research subject (Table 2).

Table 2. Description of SYNTAX Score in research subject

	All subjects	Diagnosis		p-value
		UAP / NSTEMI (n=33)	STEMI (n=43)	
SYNTAX score (mean ± SD)	24 (3-55)	24 (9-55)	23 (3-50.5)	0.949

Table 2 showed there was no difference of SYNTAX score between NSTEMI and STEMI ($p>0.05$).

Relationship between SYNTAX Score and ApoE Allele (Table 3).

Table 3. Relationship between SYNTAX Score and ApoE Allele

	ApoE23 (n= 2)	ApoE24 (n= 3)	ApoE33 (n= 35)	ApoE34 (n = 13)	ApoE44 (n = 1)	p-value
SYNTAX score (mean ± SD)	17 ± 16.9	21.2 ± 1.3	24.9 ± 12.8	25 ± 8.6	16	0.591

Table 3 showed the relationship between the SYNTAX score and the ApoE genotype did not have a significant difference. However, The SYNTAX score of the ApoE34 genotype has the highest value compared to other genotypes.

Frequency of ApoE genotype in CHD patients (Table 4).

Table 4. Frequency of ApoE genotype in CHD patients

Genotype	Quantity	ApoE Genotype (%)
ε2/ε2	0	0.00%
ε2/ε3	2	3.70%
ε2/ε4	3	5.56%
ε3/ε3	35	64.81%
ε3/ε4	13	24.07%
ε4/ε4	1	1.85%
Total	54	100.00%

Table 4 found that the most frequency of ApoE alleles in CHD patients was 3/ε3 (64.81%). Frequency of ApoE allele in CHD patients (Figure 2).

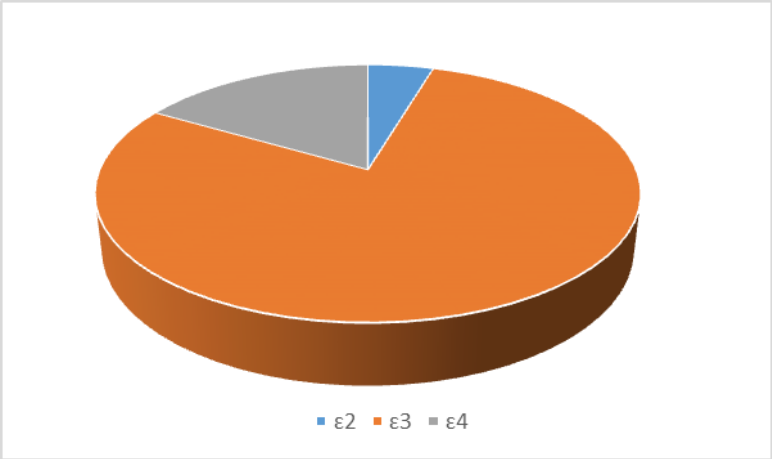

Figure 2. Frequency of ApoE allele in CHD patients

Figure 2 found the ApoE genotype frequency in CHD patients is E22 = 0%, E23 = 3.70%, E24 = 5.56%, E33 = 64.81%, E34 = 24.07%, and E44 = 1.85%

IV. DISCUSSION

Coronary Heart Disease is a complex disease and is influenced by many factors carried by genetic and environmental factors. Although the clinical management of coronary heart disease is increasing, there are still reports that CHD is the main disease that causes adults to die in this world (Xu et al., 2014). Dyslipidemia factor strongly affects CHD in this study. The increase in trigleserides, LDL, and low HDL levels makes dyslipidemia (88.6%) the main factor for CHD in smoking (74.1%), hypertension (57.3%), family history (14.8%), and menopause (3.7%). The total cholesterol value in this study showed a normal number of <200 mg / dl (188.6 + 64.5 mg / dl), the level of triglycerides in CHD was still normal at <150 mg / dl (134.7 + 49.9 mg / dl), but LDL levels increased> 100 mg / dl (125.03 + 50.5 mg / dl) and decreased HDL levels <45 mg / dl (38.5 (14-87) mg / dl).

LDL and CHD are associated with the process of atherosclerosis. The beginning of the process of atherosclerosis is the presence of damage or endothelial dysfunction in the arterial wall. Endothelial damage is likely to occur due to an increase in LDL. When LDL levels are high, the cholesterol carried by LDL will settle in the subendothelial layer.

The average age of patients studied in this study is quite high, namely 57.15 + 5.27 years and is more common in male gender (90.7%) compared to women (9.3%).

ApoE is a functional polypomorphism protein and encoded by three alleles, e2 (Cys112 / Cys158), e3 (Cys112 / Arg158), and e4 (Arg112 / Arg158). Each ApoE isoform has a different effect on lipoprotein metabolism. There are differences in lipid levels in the ApoE gene allele (Figure.1). ApoE4 alleles have the highest lipid levels compared to ApoE2 and ApoE3. ApoE4 alleles 40 - 50% are at higher risk of carrying CHD (Perki, 2015). Homozygosity in ApoE4 (e4 / e4) will increase the risk further. This is because of the high ability of e4 to bind LDL-C and can even occur at a young age, and LDL-C can increase with age (Haan et al., 2010).

The frequency of ApoE alleles in CHD patients is e2 = 4.63%, e3 = 78.70%, and e4 = 16.67% (Table 4) and the ApoE genotype frequency in CHD patients is E22 = 0%, E23 = 3.70%, E24 = 5.56%, E33 = 64.81%, E34 = 24.07%, and E44 = 1.85% (Figure 2). Compared with the research conducted in 2016 namely e2 = 6.5%, e3 = 85.5%, and e4 = 8% with ApoE gene distribution E22 = 0%, E23 = 12%, E24 = 1 %, E33 = 73%, E34 = 12%, and E44 = 2% (Sianos et al., 2005). There are similarities in the study that e3 allele has the highest value compared to e2 and e4 alleles. ApoE genotype distribution has similarities in the high level of E33 compared to other genotypes. ApoE33 is found in normal populations and patients with CHD,

The relationship between the SYNTAX score and the ApoE genotype did not have a significant difference. However, The SYNTAX score of the ApoE34 genotype has the highest value compared to other genotypes (Table 3).

The use of statins to reduce LDL-C levels, prevention of CHD, and the possibility of stroke has increased in the last 10-15 years. Statins are very effective in reducing LDL-C and also the effects of inflammation. There is still little research on the effectiveness of statin therapy on e4 alleles compared to e2 or e3 alleles (Haan et al., 2010; Song et al., 2004). In this study, statin therapy had the most effect on e3 which was ancestor alleles (wild type) and had the least effect on e4.

V. CONCLUSION

Dyslipidemia, smoking and hypertension factors are the main risk factors for non-diabetic acute coronary syndrome patients. Obtained SYNTAX score (median, min-max) in patients with acute non-diabetic coronary syndrome, 24 (3-55). There were no significant median differences in SYNTAX scores between STEMI and NSTEMI patients. The relationship between the SYNTAX score and the ApoE genotype has no significant difference. ApoE3 / 4 genotype has the highest SYNTAX score and the e4 allele has the most influence on CHD despite the influence of statin therapy.

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